Summary of Product Characteristics

VORAY 20 mg

(Vortioxetine 20 mg Film-Coated Tablets)

1 Name of the medicinal product

VORAY 20 mg – Vortioxetine 20 mg Film-Coated Tablets

2 Qualitative and quantitative composition

Each film-coated tablet contains vortioxetine hydrobromide equivalent to 20 mg vortioxetine.

Excipient(s) with known effect
Each film-coated tablet contains mannitol. This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is toP say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3 Pharmaceutical form

Film-coated tablet.

4 Clinical particulars

4.1 Therapeutic indications

VORAY 20 mg is indicated for the treatment of major depressive episodes in adults.

4.2 Posology and method of administration

Posology
The starting and recommended dose of vortioxetine is 10 mg once daily in adults less than 65 years of age.

Depending on individual patient response, the dose may be increased to a maximum of 20 mg vortioxetine once daily, or decreased to a minimum of 5 mg vortioxetine once daily.

After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response.

Treatment discontinuation
A gradual reduction in dosage may be considered to avoid the occurrence of discontinuation symptoms (see section 4.8). However, there are insufficient data to provide specific recommendations for a tapering schedule.

Special populations

Elderly patients
The lowest effective dose of 5 mg vortioxetine once daily should always be used as the starting dose in patients ≥ 65 years of age. Caution is advised when treating patients ≥ 65 years of age with doses higher than 10 mg vortioxetine once daily, for which data are limited (see section 4.4).

Cytochrome P450 inhibitors
Depending on individual patient response, a lower dose of vortioxetine may be considered if a strong CYP2D6 inhibitor (for example bupropion, quinidine, fluoxetine, paroxetine) is added to vortioxetine treatment (see section 4.5).

Cytochrome P450 inducers

Depending on individual patient response, a dose adjustment of vortioxetine may be considered if a broad cytochrome P450 inducer (for example rifampicin, carbamazepine, phenytoin) is added to vortioxetine treatment (see section 4.5).

Paediatric population
VORAY 20 mg should not be used in paediatric patients (under 18 years of age) with major depressive disorder, because efficacy has not been demonstrated (see section 5.1). The safety of vortioxetine in paediatric patients is described in sections 4.4, 4.8 and 5.1.

Renal or hepatic impairment
No dose adjustment is needed based on renal or hepatic function (see sections 4.4 and 5.2).

Method of administration
VORAY 20 mg is for oral use. The film-coated tablets can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concomitant use with non-selective monoamine oxidase inhibitors (MAOIs) or selective MAO-A inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Use in paediatric population
VORAY 20 mg should not be used in children and adolescents aged 7 to 17 years with major depressive disorder, because efficacy has not been demonstrated (see section 5.1). In general, the adverse reaction profile of vortioxetine in children and adolescents was similar to that seen in adults, except for a higher incidence of abdominal pain-related events and, in adolescents specifically, a higher incidence of suicidal ideation compared with adults (see sections 4.8 and 5.1).

In clinical studies in children and adolescents treated with antidepressants, suicide-related behaviour (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour, anger) were more frequently observed than in those treated with placebo.

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical studies of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared with placebo in patients less than 25 years old.

Close supervision of patients, and in particular of those at high risk, should accompany treatment, especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behaviour or thoughts, and unusual changes in behaviour, and to seek medical advice immediately if these symptoms present.

Seizures

Seizures are a potential risk with antidepressants. Vortioxetine should therefore be introduced cautiously in patients who have a history of seizures or who have unstable epilepsy (see section 4.5). Treatment should be discontinued in any patient who develops seizures, or for whom there is an increase in seizure frequency.

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS)
Serotonin Syndrome or Neuroleptic Malignant Syndrome, potentially life-threatening conditions, may occur with vortioxetine. The risk of SS or NMS is increased with concomitant use of serotonergic-active substances (including opioids and triptans), medicinal products that impair the metabolism of serotonin (including MAOIs), antipsychotics, and other dopamine antagonists. Patients should be monitored for the emergence of signs and symptoms of SS or NMS (see sections 4.3 and 4.5).

Serotonin Syndrome symptoms include mental status changes (for example agitation, hallucinations, coma), autonomic instability (for example tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (for example hyperreflexia, incoordination) and/or gastrointestinal symptoms (for example nausea, vomiting, diarrhoea). If this occurs, treatment with vortioxetine should be discontinued immediately and symptomatic treatment should be initiated.

Mania/hypomania
Vortioxetine should be used with caution in patients with a history of mania or hypomania, and should be discontinued in any patient entering a manic phase.

Aggression/agitation
Patients treated with antidepressants, including vortioxetine, may also experience feelings of aggression, anger, agitation and irritability. The patient's condition and disease status should be closely monitored. Patients (and caregivers of patients) should be alerted to seek medical advice if aggressive or agitated behaviour emerges or worsens.

Haemorrhage
Bleeding abnormalities, such as ecchymoses, purpura and other haemorrhagic events such as gastrointestinal or gynaecological bleeding, have been reported rarely with the use of antidepressants with serotonergic effect, including vortioxetine. SSRIs and SNRIs may increase the risk of postpartum haemorrhage, and this risk could potentially apply also to vortioxetine (see section 4.6). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (for example atypical antipsychotics and phenothiazines, most tricyclic antidepressants, non-steroidal anti-inflammatory drugs, acetylsalicylic acid) (see section 4.5), and in patients with known bleeding tendencies or disorders.

Hyponatraemia
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely with the use of antidepressants with serotonergic effect (SSRIs, SNRIs). Caution should be exercised in patients at risk, such as the elderly, patients with cirrhosis of the liver, or patients concomitantly treated with medicinal products known to cause hyponatraemia. Discontinuation of vortioxetine should be considered in patients with symptomatic hyponatraemia, and appropriate medical intervention should be instituted.

Glaucoma
Mydriasis has been reported in association with the use of antidepressants, including vortioxetine. This mydriatic effect has the potential to narrow the eye angle, resulting in increased intraocular pressure and angle-closure glaucoma. Caution is advised when prescribing vortioxetine to patients with increased intraocular pressure, or to those at risk of acute narrow-angle glaucoma.

Elderly

Data on the use of vortioxetine in elderly patients with major depressive episodes are limited. Caution should therefore be exercised when treating patients ≥ 65 years of age with doses higher than 10 mg vortioxetine once daily (see sections 4.2, 4.8 and 5.2).

Renal or hepatic impairment
Given that subjects with renal or hepatic impairment are vulnerable, and that the data on the use of vortioxetine in these subpopulations are limited, caution should be exercised when treating these patients (see sections 4.2 and 5.2).

Excipients
This medicinal product contains mannitol, which may have a mild laxative effect.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Vortioxetine is extensively metabolised in the liver, primarily through oxidation catalysed by CYP2D6 and to a minor extent by CYP3A4/5 and CYP2C9 (see section 5.2).

Potential for other medicinal products to affect vortioxetine

Irreversible non-selective MAOIs
Due to the risk of serotonin syndrome, vortioxetine is contraindicated in any combination with irreversible non-selective MAOIs. Vortioxetine must not be initiated for at least 14 days after discontinuation of treatment with an irreversible non-selective MAOI, and must be discontinued for at least 14 days before starting treatment with an irreversible non-selective MAOI (see section 4.3).

Reversible, selective MAO-A inhibitor (moclobemide)
The combination of vortioxetine with a reversible and selective MAO-A inhibitor, such as moclobemide, is contraindicated (see section 4.3). If the combination proves necessary, the added medicinal product should be given at minimum dosage and under close clinical monitoring for serotonin syndrome (see section 4.4).

Reversible, non-selective MAOI (linezolid)
The combination of vortioxetine with a weak reversible and non-selective MAOI, such as the antibiotic linezolid, is contraindicated (see section 4.3). If the combination proves necessary, the added medicinal product should be given at minimum dosage and under close clinical monitoring for serotonin syndrome (see section 4.4).

Irreversible, selective MAO-B inhibitor (selegiline, rasagiline)
Although a lower risk of serotonin syndrome is expected with selective MAO-B inhibitors than with MAO-A inhibitors, the combination of vortioxetine with irreversible MAO-B inhibitors, such as selegiline or rasagiline, should be administered with caution. Close monitoring for serotonin syndrome is necessary if used concomitantly (see section 4.4).

Serotonergic medicinal products
Co-administration of medicinal products with serotonergic effect, for example opioids (including tramadol) and triptans (including sumatriptan), may lead to serotonin syndrome (see section 4.4).

St John's wort
Concomitant use of antidepressants with serotonergic effect and herbal remedies containing St John's wort (Hypericum perforatum) may result in a higher incidence of adverse reactions, including serotonin syndrome (see section 4.4).

Medicinal products lowering the seizure threshold

Antidepressants with serotonergic effect can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold, for example antidepressants (tricyclics, SSRIs, SNRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol (see section 4.4).

Electroconvulsive therapy (ECT)
There is no clinical experience with concurrent administration of vortioxetine and ECT; caution is therefore advisable.

CYP2D6 inhibitors
Exposure to vortioxetine increased 2.3-fold for area under the curve (AUC) when vortioxetine 10 mg/day was co-administered with bupropion (a strong CYP2D6 inhibitor, 150 mg twice daily) for 14 days in healthy subjects. Co-administration resulted in a higher incidence of adverse reactions when bupropion was added to vortioxetine than when vortioxetine was added to bupropion. Depending on individual patient response, a lower dose of vortioxetine may be considered if a strong CYP2D6 inhibitor (for example bupropion, quinidine, fluoxetine, paroxetine) is added to vortioxetine treatment (see section 4.2).

CYP3A4, CYP2C9 and CYP2C19 inhibitors
When vortioxetine was co-administered following 6 days of ketoconazole 400 mg/day (a CYP3A4/5 and P-glycoprotein inhibitor), or following 6 days of fluconazole 200 mg/day (a CYP2C9, CYP2C19 and CYP3A4/5 inhibitor), in healthy subjects, a 1.3-fold and 1.5-fold increase respectively in vortioxetine AUC was observed. No dose adjustment is needed. No inhibitory effect of a 40 mg single dose of omeprazole (a CYP2C19 inhibitor) was observed on the multiple-dose pharmacokinetics of vortioxetine in healthy subjects.

Interactions in CYP2D6 poor metabolisers
Co-administration of strong inhibitors of CYP3A4 (such as itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, conivaptan and many of the HIV protease inhibitors) and inhibitors of CYP2C9 (such as fluconazole and amiodarone) to CYP2D6 poor metabolisers (see section 5.2) has not been investigated specifically, but it is anticipated that it will lead to a more marked increase in exposure to vortioxetine in these patients compared with the moderate effect described above. Depending on individual patient response, a lower dose of vortioxetine may be considered if a strong inhibitor of CYP3A4 or CYP2C9 is co-administered in CYP2D6 poor metabolisers.

Cytochrome P450 inducers
When a single 20 mg dose of vortioxetine was co-administered following 10 days of rifampicin 600 mg/day (a broad inducer of CYP isozymes) in healthy subjects, a 72% decrease in the AUC of vortioxetine was observed. Depending on individual patient response, a dose adjustment may be considered if a broad cytochrome P450 inducer (for example rifampicin, carbamazepine, phenytoin) is added to vortioxetine treatment (see section 4.2).

Alcohol
No effect on the pharmacokinetics of vortioxetine or ethanol, and no significant impairment in cognitive function relative to placebo, were observed when vortioxetine in a single dose of 20 mg or 40 mg was co-administered with a single dose of ethanol (0.6 g/kg) in healthy subjects. However, alcohol intake is not advisable during antidepressant treatment.

Acetylsalicylic acid
No effect of multiple doses of acetylsalicylic acid 150 mg/day on the multiple-dose pharmacokinetics of vortioxetine was observed in healthy subjects.

Potential for vortioxetine to affect other medicinal products

Anticoagulants and antiplatelet medicinal products
No significant effects relative to placebo were observed in INR, prothrombin or plasma R-/S-warfarin values following co-administration of multiple doses of vortioxetine with stable doses of warfarin in healthy subjects. No significant inhibitory effect relative to placebo on platelet aggregation, or on the pharmacokinetics of acetylsalicylic acid or salicylic acid, was observed when acetylsalicylic acid 150 mg/day was co-administered following multiple doses of vortioxetine. However, caution should be exercised when vortioxetine is combined with oral anticoagulants, antiplatelet medicinal products, or medicines used for pain relief (for example acetylsalicylic acid or NSAIDs), due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction (see section 4.4).

Cytochrome P450 substrates
In vitro, vortioxetine did not show any relevant potential for inhibition or induction of cytochrome P450 isozymes (see section 5.2). Following multiple doses of vortioxetine, no inhibitory effect was observed in healthy subjects for the cytochrome P450 isozymes CYP2C19 (omeprazole, diazepam), CYP3A4/5 (ethinylestradiol, midazolam), CYP2B6 (bupropion), CYP2C9 (tolbutamide, S-warfarin), CYP1A2 (caffeine) or CYP2D6 (dextromethorphan).

No pharmacodynamic interactions were observed. No significant impairment in cognitive function relative to placebo was observed for vortioxetine following co-administration with a single 10 mg dose of diazepam. No significant effects relative to placebo were observed in the levels of sex hormones following co-administration of vortioxetine with a combined oral contraceptive (ethinylestradiol 30 micrograms / levonorgestrel 150 micrograms).

Lithium, tryptophan
No clinically relevant effect was observed during steady-state lithium exposure following co-administration with multiple doses of vortioxetine in healthy subjects. However, there have been reports of enhanced effects when antidepressants with serotonergic effect have been given together with lithium or tryptophan; concomitant use of vortioxetine with these medicinal products should therefore be undertaken with caution.

Interference with urine drug screens
There have been reports of false positive results in urine enzyme immunoassays for methadone in patients who have taken vortioxetine. Caution should be exercised in the interpretation of positive urine drug screen results, and confirmation by an alternative analytical technique (for example chromatographic methods) should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of vortioxetine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

The following symptoms may occur in the newborn after maternal use of a serotonergic medicinal product in the later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either discontinuation effects or excess serotonergic activity. In the majority of instances, such complications began immediately or soon (less than 24 hours) after delivery.

Epidemiological data suggest that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN with vortioxetine treatment, this potential risk

cannot be ruled out, taking into account the related mechanism of action (increase in serotonin concentrations).

VORAY 20 mg should only be administered to pregnant women if the expected benefits outweigh the potential risk to the foetus.

Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following exposure to an SSRI or SNRI within the month prior to birth. Although no studies have investigated an association between vortioxetine treatment and postpartum haemorrhage, there is a potential risk, taking into account the related mechanism of action (see section 4.4).

Breast-feeding

Available data in animals have shown excretion of vortioxetine and its metabolites in milk. It is expected that vortioxetine will be excreted into human milk (see section 5.3). A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from VORAY 20 mg treatment, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Fertility studies in male and female rats showed no effect of vortioxetine on fertility, sperm quality or mating performance (see section 5.3). Human case reports with medicinal products from the related pharmacological class of antidepressants (SSRIs) have shown an effect on sperm quality that is reversible. An impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

VORAY 20 mg has no or negligible influence on the ability to drive and use machines. However, as adverse reactions such as dizziness have been reported, patients should exercise caution when driving or operating hazardous machinery, especially when starting treatment with vortioxetine or when changing the dose.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction was nausea.

Tabulated list of adverse reactions

Adverse reactions are listed below using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). The list is based on information from clinical trials and post-marketing experience.

System Organ Class	Frequency	Adverse reaction
Immune system disorders	Not known*	Anaphylactic reaction
Endocrine disorders	Not known*	Hyperprolactinaemia, in some cases associated with galactorrhoea
Metabolism and nutrition disorders	Not known*	Hyponatraemia
Psychiatric disorders	Common	Abnormal dreams
	Uncommon	Hallucinations
	Not known*	Insomnia; agitation, aggression (see section 4.4)
Nervous system disorders	Common	Dizziness
	Uncommon	Tremor
	Not known*	Serotonin syndrome, headache, akathisia, bruxism, trismus, restless legs syndrome
Eye disorders	Uncommon	Blurred vision

System Organ Class	Frequency	Adverse reaction
	Rare	Mydriasis (which may lead to acute narrow-angle glaucoma – see section 4.4)
Vascular disorders	Uncommon	Flushing
	Not known*	Haemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal bleeding)
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, constipation, vomiting, dyspepsia
Skin and subcutaneous tissue disorders	Common	Pruritus, including generalised pruritus; hyperhidrosis
	Uncommon	Night sweats
	Not known*	Angioedema, urticaria, rash
Reproductive system and breast disorders	Not known*	Sexual dysfunction
General disorders and administration site conditions	Not known*	Discontinuation syndrome

* Based on post-marketing cases.

Description of selected adverse reactions

Nausea

Nausea was usually mild or moderate and occurred within the first two weeks of treatment. The reactions were usually transient and did not generally lead to cessation of therapy. Gastrointestinal adverse reactions, such as nausea, occurred more frequently in women than in men.

Elderly patients

For doses ≥ 10 mg vortioxetine once daily, the withdrawal rate from the studies was higher in patients aged ≥ 65 years. For doses of 20 mg vortioxetine once daily, the incidences of nausea and constipation were higher in patients aged ≥ 65 years (42% and 15% respectively) than in patients aged < 65 years (27% and 4% respectively) (see section 4.4).

Sexual dysfunction

In clinical studies, sexual dysfunction was assessed using the Arizona Sexual Experience Scale (ASEX). Doses of 5 to 15 mg showed no difference to placebo. However, the 20 mg dose of vortioxetine was associated with an increase in treatment-emergent sexual dysfunction (see section 5.1). In the post-marketing setting, cases of sexual dysfunction have also been reported with doses of vortioxetine below 20 mg.

Class effect

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving a medicinal product from the related pharmacological classes of antidepressants (SSRIs or TCAs). The mechanism behind this risk is unknown, and it is not known whether this risk is also relevant for vortioxetine.

Paediatric population

A total of 304 children aged 7 to 11 years and 308 adolescents aged 12 to 17 years with major depressive disorder were treated with vortioxetine in two double-blind, placebo-controlled studies respectively. In general, the adverse reaction profile of vortioxetine in children and adolescents was similar to that observed in adults, except for a higher incidence of abdominal pain-related events and, in adolescents specifically, a higher incidence of suicidal ideation compared with adults (see section 5.1).

Symptoms upon discontinuation of vortioxetine treatment

In the clinical studies, discontinuation symptoms were systematically evaluated following abrupt cessation of vortioxetine treatment. There was no clinically relevant difference to placebo in the incidence or nature of the discontinuation symptoms after treatment with vortioxetine (see section

5.1). Cases describing discontinuation symptoms have been reported in the post-marketing setting and have included symptoms such as dizziness, headache, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia), nausea and/or vomiting, anxiety, irritability, agitation, fatigue and tremor. These symptoms may occur within the first week of vortioxetine discontinuation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the National Regulatory Authority.

4.9 Overdose

Ingestion of vortioxetine in clinical trials in the dose range of 40 mg to 75 mg has caused an aggravation of the following adverse reactions: nausea, postural dizziness, diarrhoea, abdominal discomfort, generalised pruritus, somnolence and flushing.

Post-marketing experience mainly concerns vortioxetine overdoses of up to 80 mg. In the majority of cases, no symptoms or mild symptoms were reported, the most frequent being nausea and vomiting. There is limited experience with vortioxetine overdoses above 80 mg; following dosages several-fold higher than the therapeutic dose range, events of seizure and serotonin syndrome have been reported.

Management of overdose should consist of treating clinical symptoms and relevant monitoring. Medical follow-up in a specialised environment is recommended.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics; other antidepressants.

ATC code: N06AX26

Mechanism of action
The mechanism of action of vortioxetine is thought to be related to its direct modulation of serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter. Non-clinical data indicate that vortioxetine is a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, a 5-HT1B receptor partial agonist, a 5-HT1A receptor agonist, and an inhibitor of the 5-HT transporter, leading to modulation of neurotransmission in several systems, including predominantly the serotonin system but probably also the noradrenaline, dopamine, histamine, acetylcholine, GABA and glutamate systems. This multimodal activity is considered responsible for the antidepressant and anxiolytic-like effects, and for the improvement of cognitive function, learning and memory observed with vortioxetine in animal studies. However, the precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear, and caution should be applied when extrapolating animal data directly to humans.

In humans, two positron emission tomography studies have been conducted using 5-HT transporter ligands (11C-MADAM or 11C-DASB) to quantify 5-HT transporter occupancy in the brain across different dose levels. The mean 5-HT transporter occupancy in the raphe nuclei was approximately 50% at 5 mg/day, 65% at 10 mg/day, and increased to above 80% at 20 mg/day.

Clinical efficacy and safety
The efficacy and safety of vortioxetine have been studied in a clinical programme that included more than 6,700 patients, of whom more than 3,700 were treated with vortioxetine in short-term (≤

12 weeks) studies of major depressive disorder. Twelve double-blind, placebo-controlled, 6- or 8-week, fixed-dose studies have been conducted to investigate the short-term efficacy of vortioxetine in adults (including the elderly). Efficacy was demonstrated with at least one dosage group across 9 of the 12 studies, showing at least a 2-point difference to placebo in the Montgomery and Åsberg Depression Rating Scale (MADRS) or the 24-item Hamilton Depression Rating Scale total score. The efficacy of vortioxetine increased with increasing dose.

In a meta-analysis of the mean change from baseline in MADRS total score at week 6/8 in the short-term, placebo-controlled studies in adults, the overall mean difference to placebo was statistically significant: −2.3 points ($p = 0.007$), −3.6 points ($p < 0.001$) and −4.6 points ($p < 0.001$) for the 5, 10 and 20 mg/day doses respectively. The proportion of responders ranged from 46% to 49% for vortioxetine versus 34% for placebo ($p < 0.01$).

Maintenance of antidepressant efficacy was demonstrated in a relapse-prevention study. Patients in remission after an initial 12-week open-label treatment period with vortioxetine were randomised to vortioxetine 5 or 10 mg/day or placebo, and observed for relapse during a double-blind period of at least 24 weeks. Vortioxetine was superior to placebo ($p = 0.004$) on the primary outcome measure, time to relapse, with a hazard ratio of 2.0.

In an 8-week, double-blind, placebo-controlled, fixed-dose study in elderly depressed patients (aged ≥ 65 years, n = 452), vortioxetine 5 mg/day was superior to placebo as measured by improvement in the MADRS and HAM-D24 total scores, with a 4.7-point difference to placebo in MADRS total score at week 8.

Vortioxetine had no effect relative to placebo on body weight, heart rate or blood pressure in clinical short- and long-term studies. No clinically significant changes were observed in hepatic or renal assessments. Vortioxetine has not shown any clinically significant effect on ECG parameters, including the QT, QTc, PR and QRS intervals; in a thorough QTc study in healthy subjects at doses up to 40 mg daily, no potential for prolongation of the QTc interval was observed.

Paediatric population

Two short-term, randomised, double-blind, placebo-controlled, fixed-dose, active-referenced efficacy and safety studies have been conducted, one in children aged 7 to 11 years and one in adolescents aged 12 to 17 years with major depressive disorder. In neither study was vortioxetine (10 or 20 mg/day) statistically significantly superior to placebo based on the Children's Depression Rating Scale-Revised total score. Vortioxetine should therefore not be used in paediatric patients (under 18 years of age) with major depressive disorder (see section 4.2).

5.2 Pharmacokinetic properties

Absorption

Vortioxetine is slowly but well absorbed after oral administration, and the peak plasma concentration is reached within 7 to 11 hours. Following multiple dosing of 5, 10 or 20 mg/day, mean Cmax values of 9 to 33 ng/ml were observed. The absolute bioavailability is 75%. No effect of food on the pharmacokinetics was observed (see section 4.2).

Distribution

The mean volume of distribution (Vss) is 2,600 litres, indicating extensive extravascular distribution. Vortioxetine is highly bound to plasma proteins (98 to 99%), and the binding appears to be independent of vortioxetine plasma concentrations.

Biotransformation

Vortioxetine is extensively metabolised in the liver, primarily through oxidation catalysed by CYP2D6 and to a minor extent by CYP3A4/5 and CYP2C9, with subsequent glucuronic acid conjugation. No inhibitory or inducing effect of vortioxetine was observed in the drug-drug

interaction studies for the CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5 (see section 4.5). Vortioxetine is a poor P-glycoprotein substrate and inhibitor. The major metabolite of vortioxetine is pharmacologically inactive.

Elimination
The mean elimination half-life and oral clearance are 66 hours and 33 l/h respectively. Approximately two-thirds of the inactive vortioxetine metabolites are excreted in the urine and approximately one-third in the faeces. Only negligible amounts of vortioxetine are excreted in the faeces. Steady-state plasma concentrations are achieved in approximately 2 weeks.

Linearity/non-linearity
The pharmacokinetics are linear and time-independent in the dose range studied (2.5 to 60 mg/day). In accordance with the half-life, the accumulation index is 5 to 6 based on AUC0-24h following multiple doses of 5 to 20 mg/day.

Special populations
Elderly: in elderly healthy subjects (aged ≥ 65 years; n = 20), exposure to vortioxetine increased by up to 27% (Cmax and AUC) compared with young healthy control subjects (aged ≤ 45 years) after multiple doses of 10 mg/day. The lowest effective dose of 5 mg vortioxetine once daily should always be used as the starting dose in patients ≥ 65 years (see section 4.2).

Renal impairment: following a single 10 mg dose of vortioxetine, renal impairment estimated using the Cockcroft-Gault formula (mild, moderate or severe; n = 8 per group) caused modest exposure increases of up to 30% compared with healthy matched controls. In patients with end-stage renal disease, only a small fraction of vortioxetine was lost during dialysis. No dose adjustment is needed based on renal function.

Hepatic impairment: the pharmacokinetics in subjects with mild, moderate or severe hepatic impairment (Child-Pugh criteria A, B or C respectively) were compared with healthy volunteers. Changes in AUC were less than 10% lower in subjects with mild or moderate hepatic impairment, and 10% higher in those with severe hepatic impairment. Changes in Cmax were less than 25% lower in all groups. No dose adjustment is needed based on hepatic function.

CYP2D6 gene types: the plasma concentration of vortioxetine was approximately two times higher in CYP2D6 poor metabolisers than in extensive metabolisers. Co-administration of strong CYP3A4/2C9 inhibitors to CYP2D6 poor metabolisers could potentially result in higher exposure (see section 4.5). In CYP2D6 ultra-rapid metabolisers, plasma concentrations of vortioxetine 10 mg/day were between those obtained in extensive metabolisers at 5 mg/day and 10 mg/day. Depending on individual patient response, a dose adjustment may be considered (see section 4.2).

Paediatric population: the pharmacokinetics of vortioxetine in paediatric patients with major depressive disorder following oral administration of 5 to 20 mg once daily were characterised using population modelling analyses. The pharmacokinetics in paediatric patients were similar to those observed in adult patients.

5.3 Preclinical safety data

Administration of vortioxetine in general toxicity studies in mice, rats and dogs was mainly associated with central nervous system-related clinical signs. These included salivation (rat and dog), pupil dilatation (dog), and two incidences of convulsions in dogs in the general toxicity study programme. A no-effect level for convulsions was established, with a corresponding safety margin of 5 considering the maximum recommended therapeutic dose of 20 mg/day. Target organ toxicity was restricted to the kidneys (rats) and liver (mice and rats). The changes in the kidney in rats (glomerulonephritis, renal tubular obstruction, crystalline material in renal tubule) and in the liver of mice and rats (hepatocellular hypertrophy, hepatocyte necrosis, bile duct hyperplasia, crystalline

material in bile ducts) were seen at exposures more than 10-fold (mice) and 2-fold (rats) the human exposure at the maximum recommended therapeutic dose of 20 mg/day. These findings were mainly attributed to rodent-specific vortioxetine-related crystalline material obstruction of the renal tubules and bile ducts respectively, and are considered of low risk to humans.

Vortioxetine was not genotoxic in a standard battery of in vitro and in vivo tests. Based on results from conventional 2-year carcinogenicity studies in mice and rats, vortioxetine is not considered to pose a risk of carcinogenicity in humans.

Vortioxetine had no effect on rat fertility, mating performance, reproductive organs, or sperm morphology and motility. Vortioxetine was not teratogenic in rats or rabbits, but reproductive toxicity in terms of effects on foetal weight and delayed ossification was seen in the rat at exposures more than 10-fold the human exposure at the maximum recommended therapeutic dose of 20 mg/day. Similar effects were seen in the rabbit at sub-therapeutic exposure. In a pre- and post-natal study in rats, vortioxetine was associated with increased pup mortality, reduced bodyweight gain and delayed pup development at doses that did not result in maternal toxicity, and with associated exposures similar to those achieved in humans following administration of vortioxetine 20 mg/day (see section 4.6). Vortioxetine-related material was distributed to the milk of lactating rats (see section 4.6). In juvenile toxicity studies in rats, all vortioxetine treatment-related findings were consistent with those noted in adult animals.

Environmental risk assessment studies have shown that vortioxetine has the potential to be persistent, bioaccumulative and toxic to the environment (risk to fish). However, at recommended patient usage, vortioxetine is considered to pose negligible risk to the aquatic and terrestrial environment (see section 6.6).

6 Pharmaceutical particulars

6.1 List of excipients

Tablet core

- Mannitol
- Microcrystalline cellulose
- Hydroxypropylcellulose
- Sodium starch glycolate (Type A)
- Magnesium stearate

Tablet coating

- Readycoat Film AQ White

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

Alu-Alu blisters containing 10 film-coated tablets. Three blisters are packed in a carton together with a package insert (30 tablets per carton).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product may pose a risk to the environment (see section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 Marketing authorisation holder

Dawa Limited

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Nairobi, Kenya

Manufacturer
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Plot No. 39-40, Ozone Industrial Park

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8 Marketing authorisation number

CTD13045 – 26669

9 Date of first authorisation/renewal of the authorisation

23.07.2026

10 Date of revision of the text

23.07.2026